ORIGINAL PAPER

UROLITHIASIS

Efficacy of combination therapy tadalafil plus tamsulosin in ureteral stents-related symptoms relief

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Introduction Ureteral stents-related symptoms (USRs) are the common complications of ureteral stenting. Tamsulosin a selective alpha-1 blocker and Tadalafil a PDE-5 inhibitor are one of drugs have been used for USRs relief. In this study we aimed to evaluate the effectiveness and safety of combination therapy Tamsulosin+Tadalafil for treating USRs comparing it with the efficacy of either Tamsulosin or Tadalafil monotherapies.

Material and methods 279 patients with indwelled unilateral ureteral stents were randomized to Tamsulosin 0.4 mg + Tadalafil 5 mg once a day (Group 1, n = 67), Tamsulosin 0.4 mg once a day (Group 2, n = 71), Tadalafil 5 mg once a day (Group 3, n = 69) and Placebo once a day (Group 4, n = 72). USRs severity was registered and calculated by using the Ureteral Symptoms Score Questionnaire (USSQ) at the 14th day of treatment. Side-effects and total analgesic use were recorded and compared.

Results At the endpoint in patients with unilateral ureteral stents the combination therapy Tamsulosin + Tadalafil led to statistically lower intensity of urinary symptoms comparing with Tamsulosin (15.2 ±4.3 vs 21.8±3.6, p = 0.0003) or Tadalafil (15.2 ±4.3 vs 20.6 ±2.8, p = 0.0004) monotherapy. All groups of treatment demonstrated significant relief of USRs comparing with Placebo mostly beneficial in the combined therapy group. Body pain and analgesic need in Group 1 was lower than in Groups 2, 3 or 4. Side-effects were registered rarely without statistical differences in frequency between groups.

Conclusions Combination therapy with Tamsulosin + Tadalafil is an effective and safe option that achieves the statistically more significant relief of USRs comparing with Tadalafil or Tamsulosin monotherapies.

Key Words: urolithiasis ‹› ureteral stents-related symptoms ‹› double J ureteral stents ‹› Tamsulosin ‹› Tadalafil ‹› combination therapy

INTRODUCTION

Along with percutaneous nephrostomy, ureteral stenting is the main wide-using method for successful elimination of the upper urinary tract obstruction different etiology [1, 2]. Long-term inserted ureteral stent as a foreign body inside of urinary tract is causing the symptoms of irritation that usually make a negative influence on quality of life in a patient [3]. Ureteral stents-related symptoms (USRs) are the common complications of ureteral stent indwelling and may occur in 80% patients or even more [4]. Tamsulosin, a selective alpha-1 blocker, is the recommended wide-using drug for relief the USRs. Last years, numerous publications informed about the impact of phosphodiesterase-5 (PDE-5) inhibitor Tadalafil, initially designed as erectile dysfunction correction drug, on USRs intensity. The effisacy of Tamsulosin and Tadalafil for elimination of USRs is comparing [5, 6].

Objectives

We aimed to evaluate the effectiveness and safety of combination therapy Tamsulosin + Tadalafil for treating USRs comparing it with the efficacy of either Tamsulosin or Tadalafil monotherapies.

MATERIAL AND METHODS

Between January 2021 to May 2023, 279 patients (178 males and 101 females) aged 38.2 ±19.7 years (range: 18–59 years) with indwelled unilateral Double J (DJ) ureteral stents were randomized to Tamsulosin 0.4 mg once a day + Tadalafil 5 mg once a day (Group 1, n = 67), Tamsulosin 0.4 mg once a day (Group 2, n = 71), Tadalafil 5mg once a day (Group 3, n = 69) and Placebo once a day (Group 4, n = 72). Simple randomization was performed and all investigators (Authors) were blinded.

The exclusion criteria were patients with short-term ureteral stenting (<14 days), fever, congenital urogenital abnormalities, confirmed urological/others oncological diseases, urethral/ureteral strictures, previous diagnosis of overactive bladder, benign prostatic hyperplasia, chronic cystitis, prostatitis and/or chronic pelvic pain, pregnant females, patients with severe liver/renal/heart failure or glaucoma. Patients who had previous stent in the past were not included into the study because of they have commonly different pain/USRs perceptions than naïve patients which is not correct for comparison and may deviate the final results.

Patient's characteristics are presented in Table 1.

All patients were underwent ureteroscopic lithotripsy with indwelling of DJ stent *in situ*. Standard 'Rüsch' DJ ureteral stents size 6 (Ch.) length 26 cm were used in all cases. Medical therapy was prescribed at once after DJ inserting and given for a period of 14–29 days (19.5 ±4.9 days, 95% CI) Patients were recommended to use Sodium Diclofenac for analgesia as *per need*. The Ureteral Stent Symptom Questionnaire (USSQ) developed by Joshi HB et al. in 2003 was the tool that has been used to access USRs severity in patients of each group and filled by every patient at the 14th day of treatment. We analyzed and calculated the survey results thereafter [7]. The safety of the treatment was evaluated as a percentage of side-effects (SEs) among patients included into each group.

Retrograde ejaculation (RE) is a well-known common side-effect of Tamsulosin. Taking into account the emerging health- and sometimes even life-threating conditions which were indications for the indwelling of ureteral stents, we did not consider RE as a significant marker for objective assessment of general health status in the stenting patients therefore we noted, but did not include this issue into the list of SEs in the Group 1 and Group 2 where Tamsulosin was prescribed.

The minimum sample size of study was determined by the clinical Effect Size (ES), variability of the outcome (standard deviation, SD), type I (α) and type II (β) error levels. Primary outcome measure of the study was urinary symptoms (US), clinically significant effect $\Delta = 3$, SD = 4 (ES = ¾ = 0.75). We were interested by the differences of outcomes for the therapies (4 groups) then $\alpha = 0.05/6 = 0.008$ (with the Bonferroni correction for 6 paired comparisons). G*Power v.3.1.9.6 was used for the sample size estimation (Means: Wilcoxon-Mann-Whitney test) [8]. At the Power = 90% minimum sample size is equal to n = 60 per group (n = 240 pts. totally). So, the power of our study was 90% and for this value our sample size was enough (n = 279 pts. totally).

The distribution of parameters was presented by: Mean ± Standard Deviation (M ±SD) for Gaussian distribution or Median (Me) and interquartile range (QI–QIII) for non-Gaussian distribution. The statistical significant difference among 4 groups was determined by ANOVA or Kruskal-Wallis test, correspondingly. For post-hoc comparisons Scheffe's or Dunn's tests, correspondingly, were used. The chi-square test was calculated to compare qualitative data. The level of significance was set at $p < 0.05$. [9]. Analysis was performed using the statistical software EZR v. 1.61 (graphical user interface for R statistical software version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria). Study was approved by the local Ethics Committee. All included patients declared their informed consent in writing.

RESULTS

At the 14th day after ureteral stent placement the combination therapy Tamsulosin + Tadalafil led to statistically lower intensity of urinary symptoms comparing with Tamsulosin (15.2 ±4.3 vs 21.8 ±3.6, p = 0.0003) or Tadalafil (15.2 ±4.3 vs 20.6 ±2.8, p = 0.0004) monotherapy. Body pain in Group 1 was lower than in Groups 2 and 3. Work performance in patients who received combination therapy was higher than in Group 2 (8.3 ±1.4 vs 10.6 ±1.3, p = 0.026) or Group 3 (8.3 ±1.4 vs 11.2 ±1.8, p = 0.018). Improvement in sexual health in groups Tadalafil and Tamsulosin + Tadalafil was similar (3.8 ±1.6 vs 3.5 ±1.3, p = 0.863) and significantly more than 6.7 ±1.4 in Tamsulosin group, p = 0.002 or 8.1 ±1.6 in Placebo group, p = 0.0006 (Table 2, Figure 1). Analgesic need was much lower in Tam-

Table 1. *Characteristics of involved patients*

Characteristic	Group 1 n = 67	Group 2 n = 71	Group 3 n = 69	Group 4 n = 72	p*
Age, yrs	36.5 ±18.3	37.4 ±19.7	38.1 ±17.6	37.2 ±15.2	0.865
M/F ratio	(44/23)	(47/24)	(42/27)	(45/27)	0.899
BMI (kg/m^2)	25.7 ±6.3	24.2 ±5.8	26.1 ±5.2	27.3 ±4.8	0.764
Stented ureter: Left/Right	36/31	32/39	34/35	33/39	0.732
ATS, days	19.6 ±4.2	18.4 ±4.1	20.5 ±6.3	19.8 ±5.4	0.627
Stone Size, cm	1.4 ±0.6	1.6 ±0.5	1.5 ±0.4	1.7 ±0.6	0.783
Comorbidity, n (%)					
Chronic pyelonephritis	18 (26.9)	20 (28.2)	19 (27.5)	22 (30.6)	0.966
Arterial hypertension	13 (19.4)	12 (16.9)	14 (20.3)	16 (22.2)	**0.583**
GERD	17 (25.4)	19 (26.8)	16 (23.2)	17 (23.6)	0.962
Chronic cholecystitis	8 (11.9)	7 (9.8)	6 (8.7)	6 (8.3)	0.892
Arthritis	7 (10.4)	8 (11.3)	5 (7.2)	7 (9.7)	**0.769**
CAD	6 (9.0)	7 (9.9)	9 (13.0)	8 (11.1)	0.880
Diabetes mellitus	5 (7.5)	6 (8.5)	6 (8.7)	4 (5.6)	**0.691**

M/F – male-to-female; BMI – body mass index; ATS – average time of stenting; GERD – gastroesophageal reflux disease; CAD – coronary artery disease; n – number
Group 1 – Tamsulosin+Tadalafil; Group 2 – Tamsulosin; Group 3 – Tadalafil; Group 4 – Placebo; * – chi-square test was used.

Table 2. *Ureteral stent symptom scores according to USSQ domains, side-effects and total analgesic use in examined patients at the 14th day of treatment*

VARIABLES		GROUP 1, Tamsulosin+ Tadalafil, n = 67	GROUP 2, Tamsulosin, n = 71	GROUP 3, Tadalafil, n = 69	GROUP 4, Placebo n = 72	p
USSQ domains	US	15 (14–16) [234]	21 (20–22) [14]	20 (18–21) [14]	36 (34–37) [123]	<0.001*
	BP	6 (5–6) [234]	13 (12–14) [134]	7 (6–8) 12[4]	18 (16–19) [123]	<0.001*
	SM	3 (2–3) [24]	6 (6–7) [13]	3 (2–4) [24]	8 (6–8) [13]	<0.001*
	GH	18 (17–18.75) [4]	18 (17–19) [4]	18 (17–19) [4]	24 (23–25) [123]	<0.001*
	AP	11 (10–12) [4]	11 (10–12) [4]	11 (10–12) [4]	18 (16–19) [123]	<0.001*
	WP	8 (7–8) [234]	10 (9–11) [14]	10 (9–11) [14]	17 (16–18) [123]	<0.001*
TAU		400	1150	600	2100	<0.001*
Side-effects, n (%)		5 (7.5)	4 (5.6)	3 (4.3)	–	0.160**
headaches		2 (3.0)	–	1 (1.4)	–	0.268**
nausea		1 (1.5)	–	1 (1.4)	–	0.548**
facial flushing		1 (1.5)	–	1 (1.4)	–	0.548**
hoarseness		–	1 (1.4)	–	–	0.401**
dizziness		1 (1.5)	1 (1.4)	–	–	0.560**
lightheadedness		–	2 (2.8)	–	–	0.117**

US – urinary symptoms score; BP – body pain score; SM – sexual matters score; GH – General health score; AP – additional problems score; WP – work performance score; TAU – Total analgesic use (Diclofenac, mg); n – number
Notes: median and interquartile range (IQR) are presented.
* – Kruskal-Wallis test was used, Dunn's test was used for post-hoc comparisons:
1 – statistically significance difference from the GROUP 1, p <0.001;
2 – statistically significance difference from the GROUP 2, p <0.001;
3 – statistically significance difference from the GROUP 3, p <0.001;
4 – statistically significance difference from the GROUP 4, p <0.001
** – chi-square test was used

sulosin + Tadalafil group as compared to both Tamsulosin (400 mg vs 1150 mg of Sodium Diclofenac, p = 0.0008) or Tadalafil (400 mg vs 600 mg of Sodium Diclofenac, p = 0.004) groups. In Placebo group the need in analgesia was even more (2100 mg of Sodium Diclofenac). Side-effects were registered rarely and totally occur in 12 (5.8%) patients with following distribution: 5 (7.5%) cases from Group: 1, 4

(5.6%) cases from Group 2 and in 3 (4.3%) cases from Group 3 without statistical differences in frequency (p = 0.160) (Table 2). Box & Wheasker plot for Ureteral stent symptom scores in our patients according to USSQ domains is presented in the Figure 1.

DISCUSSION

Inserting of DJ stents is a routine procedure using for more than 50 yrs that aimed to prevent/eliminate the upper urinary tract obstruction different etiology [10]. USRs are famous complications of ureteral stenting that significantly reduce the quality of life in patients [3]. So, after beginning of ureteral stents using numerous drugs like different analgesics, alpha-blockers and antimuscarinics were proposed to reduce USRs with different degrees of beneficial results [11, 12]. It had been considered that above-mentioned drugs cause ureteric relaxation thereby lead to reducing the pressure transmitted toward the renal cavity during micturition, decrease the top contraction pressure leading to dilatation of ureter and lessen the irritation of bladder with the intravesical part of the stent that caused relief of USRs [13, 14].

Recently have begun to appear the data on the effectiveness of Tadalafil alone and its combination with Tamsulosin on renal calculus clearance after shock wave lithotripsy [15]. Efficacy of tamsulosin versus tadalafil as medical expulsive therapy on stone expulsion in patients with distal ureteral stones is studying [16]. Researchers suggested that Tadalafil can dilate ureters promoting the passage of ureteral calculus.

Farshi Haghro A et al. in 2019 informed that daily use of Tadalafil 10 mg relieves USRs, sexual status and decrease pain comparing with placebo, so it can be used as a new treatment option in the alleviation of lower urinary tract symptoms and can improve the quality of life in patients with DJ stents [17].

According to Balaji AR et al, 2020, Tadalafil can also be used for USRs relief and is as effective as

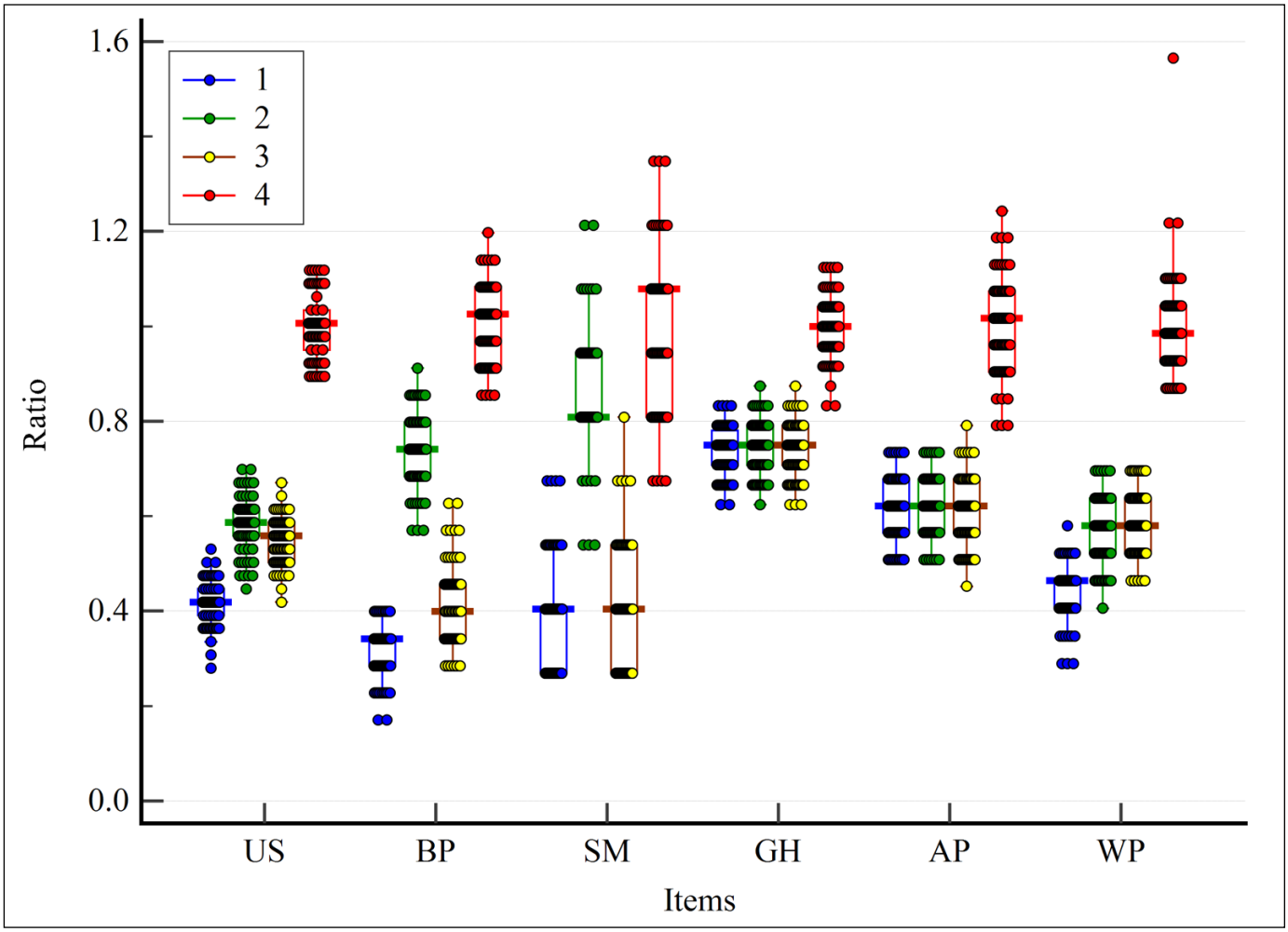

Figure 1. *Box & Wheasker plot for Ureteral stent symptom scores according to USSQ domains in Groups 1–4.*

α-blockers and antimuscarinics in relieving urinary symptoms and is more efficacious in relieving body pain and sexual symptoms [18].

In 2021 Ilyas MRF et al. informed that Tadalafil 10 mg demonstrate significantly better results compared to Tamsulosin 0.4 mg in improving USRs [5]. It is common knowledge that PDE-5 receptors are present in the lower part of ureter, bladder trigone and neck. Because of the PDE-5 receptors are there, Tadalafil a famous PDE-5 inhibitor, reducing spasms and reflux thereby eliminates urinary tract obstruction that can overcome irritation symptoms [19, 20]. Pecoraro A et al. in 2023 summarized that PDE-5 inhibitors are comparable to alpha antagonists, except for a higher improvement of sexual index of the USSQ scores [21]

Bhattar R. et al. informed that Tadalafil and Silodosin relax ureteral smooth muscle that helps in forward propagation of large size ureteroscopes without any high risk of complications or SEs. As for us, one of the main principal and significant results of research was the fact that ureteral orifices were found to be dilated in 69.6% Silodosin group, 60.9% in Tadalafil group, and only 28.6% in placebo group. A large number of patients in groups Silodosin and Tamsulosin had dilated ureteral orifices as compared to the patients in placebo group, whereas difference in visualization of ureteral orifice was statistically insignificant in Silodosin and Tadalafil groups [22]. Presented study clearly demonstrates that Tadalafil has the opportunity to relax the ureter muscles and dilate the ureter as a consequence. This feature can explain the effects of Tadalafil in relief of USRs as well as in promotion of stones passage through the ureter [15, 16].

Our prospective placebo controlled double blinded randomized study demonstrates the efficacy of combination therapy Tamsulosin + Tadalafil for ureteral stents-related symptoms relief comparing with monotherapies by both drugs. We also registered significantly less intensity of USRs in Tadalafil or Tamsulosin monotherapy groups comparing with Placebo. At the 14th day of treatment urinary symptoms in both groups of monotherapy were the same intensity and less than in Placebo group. It should be noted that general health in all groups of treatment was the same and better that in Placebo group (Table 2, Figure 1). Side effects in all three groups of treatment were noted rarely and the same in frequency. Obtained results advocate the expediency of prescribing the effective and safe Tamsulosin + Tadalafil combination therapy for USRs relief in patients with ureteral stents.

We consciously excluded RE from the list of side effects of pharmacotherapy. In our opinion, unlike other unwanted/allergic/somatic *phenomena*, this intimate and only functional parameter does not affect the state of somatic health of patients. That is why RE cannot be considered as a significant SE determining the choice for use any drug in patients with ureteral stents, which a priori must be indwelled to eliminate health/life-threating urinary tract obstruction [23].

We also excluded from the study patients who had previous stenting in the past because of they usually have more intensive pain/USRs perceptions than naïve patients that may deviate total results. In our opinion the additional research of the efficacy combination therapy Tamsulosin + Tadalafil for USRs relief in such repeatedly stented patients is needed.

To our knowledge, this is the first report of the effectiveness of proposed combination Tamsulosin + Tadalafil in ureteral stents-related symptoms relief in patients who underwent ureteral stenting. Presented study has one principal limitation. We investigated the efficacy of intake the dosage 5 mg of Tadalafil only. Considering the presence of 2.5 mg Tadalafil tablets at the pharmacological market, it would be interesting to study the efficacy 2.5 mg, or 7.5 mg in combinations with Tamsulosin 0.4 mg for USRs management. That approach might be promising direction of future investigations.

CONCLUSIONS

Our study shows that combination therapy with Tamsulosin + Tadalafil is an effective and safe option that achieves the statistically more significant relief of ureteral stents-related symptoms comparing with Tadalafil or Tamsulosin monotherapies in patients with inserted ureteral DJ stents. Work performance in examined patients who received combination therapy was higher than in all groups of comparing, while their body pain and analgesic need was much lower.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest. The authors declare no financial support and/or external funding.

ETHICS APPROVAL

Study has received approval from the Institutional Ethic's Committee.

Patients provided written consent for all procedures and study inclusion.

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